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PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

See Notification of Aransmittal of International Preliminary Examination Report (Form PCT/IPEA/416) Applicant's or agent's file reference FOR FURTHER ACTION N 1931-1 WO Priority date (day/month/year) International filing date (day/month/year) International application No. 22.06.1998 16.06.1999 PCT/SE99/01075 International Patent Classification (IPC) or national classification and IPC7 CO7C 279/12, CO7C 275/28, CO7D 295/135, A61K 51/00, A61K 49/00, A61K 31/17, A61K 31/40 Applicant AstraZeneca AB et al

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.			
2. This REPORT consists of a total of 6 sheets, including this cover sheet.			
This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).			
These annexes consist of a total of sheets.			
3. This report contains indications relating to the following items:			
I Basis of the report			
II Priority			
III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability			
IV Lack of unity of invention			
V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citation and explanations supporting such statement			
VI Certain documents cited			
VII Certain defects in the international application			
VIII Certain observations on the international application			
Date of submission of the demand	Date of completion of this report		
18.01.2000	18.09.2000		
Name and mailing address of the IPEA/SE	Authorized officer		
Patent- och registreringsverket Telex Box 5055 17978			
S-102 42 STOCKHOLM PATOREG-S Gerd Strandell/GH			
Facsimile No. 08-667 72 88 Telephone No. 08-782 25 00			

Form PCT/IPEA/409 (cover sheet) (January 1994)

International application No.

PCT/SE99/01075

I. Basis of the report		
1. This report has been drawn o under Article 14 are referred to it	n the basis of (Replacement so n this report as "originally filed	heets which have been furnished to the receiving Office in response to an invitation d" and are not annexed to the report since they do not contain amendments.):
the internationa	l application as originally fi	iled.
the description,	pages	, as originally filed,
		, filed with the demand,
	pages	, filed with the letter of,
	pages	, filed with the letter of
the claims,	Nos.	_ , as originally filed,
	Nos.	_ , as amended under Article 19,
		, filed with the demand,
		, filed with the letter of,
	Nos.	, filed with the letter of
the drawings,	sheets/fig	_ , as originally filed,
		, filed with the demand
		, filed with the letter of,
	sheets/fig	, filed with the letter of
2. The amendments have resulte	ed in the cancellation of	
the description,		
<u></u>		-
the claims,	Nos.	_
the drawings,	sheets/fig	_
This report has been e	established as if (some of) the	ne amendments had not been made, since they have been considered to go
		supplemental Box (Rule 70.2(c)).
4 Additional absorbations if n		
4. Additional observations, if n	ecessary:	
		i

International application No.

PCT/SE99/01075

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:
the entire international application,
claims Nos. 15, 20-22
because:
the said international application, or the said claims Nos. 15, 20-22
relate to the following subject matter which does not require an international preliminary examination (specify):
See PCT Rule 67.1.(iv).: Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.
the description, claims or drawings (indicate particular elements below) or said claims Nos.
are so unclear that no meaningful opinion could be formed (specify):
the claims, or said claims Nos. are so inadequately supported
by the description that no meaningful opinion could be formed.
no international search report has been establised for said claims Nos.

International application No.

PCT/SE99/01075

V. Resoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

 1. Statement
 Novelty (N)
 Claims 2-14,16-19 YES Claims 1
 YES NO

 Inventive step (IS)
 Claims 11,12 YES Claims 1-10,13,14,16-19 NO
 YES NO

Industrial applicability (IA)

Claims

1-14,16-19

Claims

NO

2. Citations and explanations

The claimed invention relates to novel 1,4-substituted phenyl compounds of the general formula (I), a process for their preparation, pharmaceutical compositions comprising the novel compounds and their use in therapy, in particular in the management of pain.

The following relevant documents are cited:

- A) WO 9639382 A1 (FUJISAWA PHARMACEUTICAL CO., LTD.), 12 December 1996 (12.12.96)
- B) EP 0507291 A1 (YOSHITOMI PHARMACEUTICAL INDUSTRIES, LTD.), 7 October 1992 (07.10.92), page 12, line 23, the claims
- C) WO 9737646 A1 (BRISTOL-MYERS SQUIBB COMPANY), 16 October 1997 (16.10.97), page 31, line 6 -line 11

Document A) discloses compounds of a general formula, which embraces compounds of claim 1 of the present application or are structurally close to the compounds according to claims 2-5. The compounds have pharmacological activities and are inter alia useful for treatment of disorders associated with spinal trauma. Thus, claim 1 is not considered to be novel. Claims 2-10, 13, 14 and 16-19, are not considered to show inventive step as what is mentioned there seems to be obvious practical measures for a person skilled in the art. The applicant has not shown that the claimed compounds are likely to have any unexpected beneficial effects compared to those in the cited document.

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International application No.

PCT/SE99/01075

Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: V

Document B) discloses therapeutically useful compounds, which are structurally close to the compounds claimed in claims 1-5 of the present application. Thus, claims 1-6, 18 and 19 are not considered to show inventive step.

Document C) discloses a compound, which is structurally close to the compounds claimed in claims 1-5 of the present application. The compound is an intermediate for preparing therapeutically useful compounds.

Consequently, the invention claimed in claim 1 is not considered to fulfil the requirements of novelty and inventive step, but is considered to fulfil the requirement of industrial applicability. The invention claimed in claims 2-14 and 16-19 is considered to fulfil the requirements of novelty and industrial applicability. The invention claimed in claims 11 and 12 is considered to fulfil the requirement of inventive step, but the invention claimed in claims 2-10, 13, 14 and 16-19 is not considered to fulfil the requirement of inventive step.

International application No.

PCT/SE99/01075

Cei	rtain published documents (Ru	e 70.10)		
	Application No. Patent No.	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (valid claim) (day/month/year)
	WO9852558	26.11.1998	21.05.199	8 23.05.1997
No	on-written disclosures (Rule 70 Kind of non-written dis	closure Date of	non-written disclosure lay/month/year)	Date of written disclosure referring to non-written disclosu (day/month/year)

Form PCT/IPEA/409 (Box VI) (January 1994)

	From the	INTERNATIONAL BU	JREAU
PCT	То:		
NOTIFICATION OF THE RECORDING OF A CHANGE (PCT Rule 92bis 1 and Administrative Instructions, Section 422) Date of mailing (day/month/year)	Global Patent	85 Södertälje	DEC 08 2000 TECH CENTER 1600/29
28 July 2000 (28.07.00)			
Applicant's or agent's file reference N 1931-1 WO		IMPORTANT NOTI	FICATION
International application No. PCT/SE99/01075	1	al filing date (day/month/yene 1999 (16.06.99)	ear)
The following indications appeared on record concerning: The applicant the inventor	the agent	the commo	n representative
Name and Address ASTRA AKTIEBOLAG S-151 85 Södertälje Sweden		State of Nationality SE Telephone No.	State of Residence SE
		Facsimile No.	
		Teleprinter No.	
2. The International Bureau hereby notifies the applicant that to the person X the name the add	_	nange has been recorded of the nationality	concerning: the residence
Name and Address ASTRAZENECA AB S-151 85 Södertälje		State of Nationality SE	State of Residence SE
Sweden		Telephone No.	
		Facsimile No.	
		Teleprinter No.	
3. Further observations, if necessary:			
4. A copy of this notification has been sent to:			
X the receiving Office		the designated Offices	concerned
the International Searching Authority	×	╡	cerned
X the International Preliminary Examining Authority	L	other:	
The International Bur au of WIPO 34, chemin d s Col mbettes 1211 Geneva 20, Switzerland	Authorized o	Beate Giffo-S	Schmitt
Facsimile No.: (41-22) 740.14.35	Telephone N	o.: (41-22) 338.83.38	

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NOTIFICATION OF THE RECORDING **OF A CHANGE**

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

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ASTRAZENECA AB Global Intellectual Property **Patents** S-151 85 Södertälje SUÈDE

RECEIVED TO THE REPORT OF THE PROPERTY OF THE PERSON OF TH

Date of mailing (day/month/year) 28 July 2000 (28.07.00)				
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Applicant's or agent's file reference	IMPORTANT NOTIFICATION			
N 1931-1 WO				
International application No. International filing date (day/month/year)				
PCT/SE99/01075	16 June 1999 (16.06.99)			
1. The following indications appeared on record concerning: the applicant the inventor	the agent the common representative			
the applicant the inventor				
Name and Address	State of Nationality State of Residence			
ASTRA AKTIEBOLAG				
Intellectual Property, Patents S-151 85 Södertälje	Telephone No.			
Sweden	+46 8 553 260 00			
Facsimile No.				
+46 8 553 288 20				
Teleprinter No.				
2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:				
the person X the name X the address the nationality the residence				
Name and Address State of Nationality State of Residence				
ASTRAZENECA AB				
Global Intellectual Property Patents Telephone No.				
S-151 85 Södertälje +46 8 553 260 00				
Sweden Facsimile No.				
,	+46 8 553 288 20			
Teleprinter No.				
3. Further observations, if necessary:				
4. A copy of this notification has been sent to:				
X the receiving Office	the designated Offices concerned			
the International Searching Authority	X the elected Offices concerned			
X the International Preliminary Examining Authority	other:			
The International Bureau f WIPO	Authorized officer			

Facsimile No.: (41-22) 740.14.35

34, chemin des Col mbettes

1211 G n va 20, Switz rland

Beate Giffo-Schmitt

Telephone No.: (41-22) 338.83.38

From the INTERNATIONAL BUREAU PCT NOTIFICATION OF THE RECORDING ASTRAZENECA AB **OF A CHANGE** Global Intellectual Property **Patents** (PCT Rule 92bis.1 and S-151 85 Södertälje Administrative Instructions, Section 422) SUÈDE Date of mailing (day/month/year) 28 July 2000 (28.07.00) Applicant's or agent's file reference IMPORTANT NOTIFICATION N 1931-1 WO International filing date (day/month/year) International application No. 16 June 1999 (16.06.99) PCT/SE99/01075 1. The following indications appeared on record concerning: the common representative the agent the applicant the inventor State of Nationality State of Residence Name and Address CA CA ASTRA PHARMA INC. 1004 Middlegate Road Mississauga, Ontario L4Y 1M4 Telephone No. Canada Facsimile No. Teleprinter No. 2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning: the residence the nationality the address the name the person State of Residence State of Nationality Name and Address CA CA ASTRAZENECA CANADA INC. 1004 Middlegate Road Telephone No. Mississauga, Ontario L4Y 1M4 Canada Facsimile No. Teleprinter No. 3. Further observations, if necessary: After the change of name as specified above, the applicant has now assigned all rights to ASTRAZENECA AB and shall therefore be deleted from the records. ASTRAZENECA AB shall now be recorded as applicant for all designated States except the United States of America.

> The Internati nal Bureau of WIPO 34, chemin d s C lombettes 1211 G n va 20, Switzerland

Authorized officer

Beate Giffo-Schmitt

Telephone No.: (41-22) 338.83.38

Facsimile No.: (41-22) 740.14.35

P/~ INT COOPERATION TREAT

	From the INTERNATIONAL BUREAU		
PCT	То:		
NOTIFICATION OF THE RECORDING OF A CHANGE (PCT Rule 92bis.1 and Administrative Instructions, Section 422) Date of mailing (day/month/year) 21 March 2000 (21.03.00)	ASTRA AKTIEBOLAG Intellectual Property, Patents S-151 85 Södertälje SUÈDE		
Applicant's or agent's file reference			
N 1931-1 WO	IMPORTANT NOTIFICATION		
International application No.	International filing date (day/month/year)		
PCT/SE99/01075	16 June 1999 (16.06.99)		
The following indications appeared on record concerning: X the applicant Name and Address PORERTS Edward	the agent the common representative State of Nationality State of Residence GB CA		
ROBERTS, Edward Astra Research Centre Montreal 7171 Fredrick-Banting St Laurent, Quebec H4S 1Z9 Consider			
Canada Facsimile No.			
	Teleprinter No.		
2. The International Bureau hereby notifies the applicant that the the person the name X the add			
Name and Address	State of Nationality State of Residence GB CH		
ROBERTS, Edward Bruderholz Allee 174 CH-4059 Basel Switzerland	Telephone No.		
Switzerrand	Facsimile No.		
	Teleprinter No.		
3. Further observations, if necessary:			
4. A copy of this notification has been sent to:			
X the receiving Office	the designated Offices concerned		
the International Searching Authority	X the elected Offices concerned		
X the International Preliminary Examining Authority	other:		
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Beate Giffo-Schmitt Telephone No.: (41, 22) 338 83 38		



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	From the INITERN	٨τι

207	From t	NE INTERNATIONAL B	UREAU
PCT	To:		
NOTIFICATION OF THE RECORDING OF A CHANGE (PCT Rule 92bis.1 and Administrative Instructions, Section 422) Date of mailing (day/month/year) 21 March 2000 (21.03.00)	Intel	RA AKTIEBOLAG lectual Property, Pater 185 Södertälje DE	ts
Applicant's or agent's file reference	 		
N 1931-1 WO		IMPORTANT NOT	FICATION
International application No. PCT/SE99/01075		onal filing date (day/month/youne 1999 (16.06.99)	ear)
The following indications appeared on record concerning: X the applicant X the inventor the agent the common representative			
Name and Address GREGOR, Vlad Alanex Corp. 3550 General Atomics Court San Diego, CA 92121 United States of America		State of Nationality US Telephone No. Facsimile No.	State of Residence US
2. The International Bureau hereby notifies the applicant that to the person the name X the ad	r	change has been recorded of the nationality	concerning:
Name and Address		State of Nationality	State of Residence
GREGOR, Vlad		US	US
12283 Carmel Vista Road # 219		Telephone No.	
San Diego, CA 92130 United States of America		Facsimile No.	
		Teleprinter No.	
3. Further observations, if necessary:			
4. A copy of this notification has been sent to:			
X the receiving Office		the designated Offices of	concerned
the International Searching Authority The International Preliminary Examining Authority	[the elected Offices conc	erned
			·
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized	officer Beate Giffo-S	chmitt
acsimile No.: (41-22) 740.14.35	Telephone I	No.: (41-22) 338.83.38	

Form PCT/IB/306 (March 1994)

PATENT COOPERATION TREATM

	From the INTERNATIONAL BUREAU
PCT	То:
NOTIFICATION OF ELECTION . (PCT Rule 61.2)	Assistant Commissioner for Patents United States Patent and Trademark Office Box PCT Washington, D.C.20231 ETATS-UNIS D'AMERIQUE
Date of mailing (day/month/year) 21 March 2000 (21.03.00)	in its capacity as elected Office
International application No. PCT/SE99/01075	Applicant's or agent's file reference N 1931-1 WO
International filing date (day/month/year) 16 June 1999 (16.06.99)	Priority date (day/month/year) 22 June 1998 (22.06.98)
Applicant	
DELORME, Daniel et al	
The designated Office is hereby notified of its election made in the demand filed with the International Preliminary 18 January 200 in a notice effecting later election filed with the International Preliminary 18 January 200 The election X was was not made before the expiration of 19 months from the priority date.	Examining Authority on: 0 (18.01.00) ational Bureau on:
Rule 32.2(b).	are of, where rule 32 applies, within the time mint under

Authorized officer

Telephone No.: (41-22) 338.83.38

Form PCT/IB/331 (July 1992)

Facsimile No.: (41-22) 740.14.35

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland

Beate Giffo-Schmitt